UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,892	02/08/2002	Alison A. McCormick	42256	1133

27860 7590 10/25/2006

LARGE SCALE BIOLOGY CORPORATION
3333 VACA VALLEY PARKWAY
SUITE 1000
VACAVILLE, CA 95688

EXAMINER	
TUNGATURTHI, PARITHOSH K	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 10/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,892	MCCORMICK ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/10/2006 has been entered.

2. Claims 1-50 have been cancelled.

Claims 51 and 55 are amended.

3. Claims 51-60 are pending and under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. This office action contains New Grounds of Rejections.

Rejections Withdrawn

6. The rejection of claim 60 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn after careful consideration of applicants arguments, please see below.

The rejection was made for reciting "allowing the vector to spread through the plant before recovering the polypeptide", because the exact meaning of the phrase is not clear. However upon reviewing the applicants arguments and careful consideration of one of ordinary skill in the art, it is understood that the phrase means that the vector is spread throughout the plant including the roots, stems, leaves, seeds, etc. Hence, the rejection is withdrawn.

7. The rejection of claim 60 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the applicants arguments.

The rejection was made because the amendments to the claim was believed to introduce NEW Matter into the claims. However, applicants argue that the support is provided in several locations in the specification (for example paragraph 76, 217, 220 and 231), wherein the specification teaches a systemic infection of the plant indicating that the vector is spread throughout the plant. Hence, the rejection is withdrawn.

New Grounds of Rejections and Response to Arguments

8. Claims 51-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 51 is not clear for reciting "a method of producing a polypeptide comprising a first and second domain comprising the steps of ..... (a) ...(b) ... and (f) screening for

a polypeptide that induces an idiotype-specific immune response directed against said polypeptide". It is unclear as to what the applicant intends the invention to be. Is the claim drawn to a method of "producing a polypeptide"? OR For a method of "screening for a polypeptide that induces an idiotype-specific immune response directed against said polypeptide", if so the claims are missing the essential steps for screening for a polypeptide. A method of producing a polypeptide as claimed in claim 51 (a) – (e) is completely different from the method of screening for a polypeptide that induces an idiotype-specific immune response directed against said polypeptide. As written, the claim consists of two distinct and independent methods. Appropriate correction is required.

9. Claims 51-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The amendments filed on 08/10/2006 introduced NEW MATTER into claim 51. The claim recites "a method of producing a polypeptide comprising a first and second domain comprising the steps of ..... (a) ...(b) ... and (f) screening for a polypeptide that induces an idiotype-specific immune response directed against said polypeptide" which is not disclosed in the specification. The specification provides support for a method of producing a polypeptide that induces an idiotype-specific response (page 13 lines 23-

25, in particular), comprising the steps (a) to (e) as recited in claim 51. However, the specification does not show or even suggest that the method of producing a polypeptide and subsequently screening for a polypeptide that induces an idiotype-specific immune response directed against said polypeptide. The response filed on 08/10/2006 does not state where the support for the amendments to claim 51 can be found. Although the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims, when filing an amendment an applicant should show support in the original disclosure for new or amended claims. See MPEP 714.02 and 2163.06 ("Applicant should specifically point out the support for any amendments made to the disclosure."). Applicants are required to specifically point our where the support for the newly added claim limitations can be found in the originally filed specification or claims or remove the limitation from the claim.

For the purposes of this office action; the claim is interpreted to be drawn to a method of producing a polypeptide, that induces an idiotype-specific immune response, comprising the steps (a) – (e) of claim 51.

10. The rejection of claims 51-60 under 35 U.S.C. 103(a) as being unpatentable over Hawkins et al (WO 94/08008, International Publication Date 14 April, 1994; IDS: January 11, 2005) in view of Fiedler et al (Immunotechnology, 3(3):205-216, October 1997; IDS: March 08, 2004) and in view of Caspar et al. (Blood, 90(9):3699-3706, November 1997; IDS: January 11, 2005) and in view of Tang et al (J. Biol Chem.

271(26):15682-15686, June 1996; IDS: January 11, 2005) and further in view of Hakim et al (J. Immunol. 157:5503-5511, 1996; IDS: January 11, 2005).is maintained.

The instant claims are interpreted to be drawn to a method of producing a single chain antibody, that induces an idiotype-specific response, comprising a first and second domain comprising the steps of: (a) joining a nucleic acid encoding the first domain of the polypeptide to a nucleic acid encoding a first part of a plurality of different linkers to produce a first nucleic acid construct; (b) joining the nucleic acid encoding a second part of the plurality of different linkers to a nucleic acid encoding the second domain of the polypeptide to produce a second nucleic acid construct; (c) incorporated said first and said second constructs into a transient plant expression vector in frame so that, when expressed, the polypeptide bears the first and second domain separated by the plurality of different linkers; (d) transfecting a plant with the vector so that the plant transiently produces the polypeptide; and (e) recovering the polypeptide' as a soluble, correctly-folded protein; wherein the first domain of said polypeptide is the Ig VH domain and the second domain is the Ig VL domain, both of which domains create an idiotype of a surface Ig of a B cell lymphoma, and wherein said polypeptide induces an idiotype-specific response directed to said lymphoma, and wherein said polypeptide induces an idiotype-specific immune response directed to said lymphoma upon administration to a subject. The method is further limited wherein the plant is a plant cell. Further, the said domains are linked by an amino acid linker that has between one and 50 residues, that consists of between one and 12 different amino acids and facilitates secretion and correct folding of said polypeptide to mimic the tumor epitope in its native form in or on

said tumor cell; wherein the plurality of different linkers are members of a randomized library of linkers that vary in size and sequence, and said library is encoded by nucleic acid sequences consisting of a repeated pattern of degenerate repeated triplet nucleotides such that position 1 of each repeated triplet cannot be the same nucleotide as position 2 of the repeated triplet, position 2 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet, or position 1 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet; further, wherein the nucleotide in the first and second positions of each repeated triplet is selected from any two of deoxyadenosine (dA), deoxyguanosine (dG), deoxycytidine (dC), and deoxythymidine (dT); and further, wherein position 1 of each repeated triplet is dA or dG, position 2 of each repeated triplet is dC or dG, and position 3 of each repeated triplet is dT.

The response filed on 05/10/2006 in addition to the arguments filed on 08/110/2006 is carefully considered, but not considered to be persuasive. Please see below.

In response to the applicant's arguments, the applicant is reminded that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5

USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

1. The applicant states that claim 51 step (c) recites "incorporating... constructs into a transient plant expression vector" and none of the references disclose a transient plant expression vector. Further, the applicants argues that "....whether or not Fiedler et al has a transient process for making scFv (a polypeptide compound) is not the same or even suggestive of the claimed method...".

In response to the above argument, the applicant is reminded of the teachings of Fiedler et al wherein Fiedler et al teach two different scFv antibodies which were expressed in plants in different plant organs and plant cell compartments have been used for the study, in addition to investigating the levels and antibody properties such as stability and antigen-binding activity (abstract, in particular).

Further, since Fiedler et al teach that the plant expression system as discussed in their studies provides not only the highest level of active single chain Fv antibodies ever reported but also a short-term storage of the foreign protein in the harvested plant material (abstract, in particular), which suggests that the plant expression system as taught by Fiedler et al still reads on the transient plant expression vector. Thus, since the expression vector as taught by Fiedler et al provides for a short-term storage of the foreign protein in the harvested plant material, it reads on the limitation as recited in claim 51 (c) and 59, which recites "transient plant expression vector" [transient meaning lasting only a short period of time, as defined by Merriam-Webster Dictionary].

2. The applicant argue that the claims do NOT recite producing any polypeptide but only those having the proper "correctly-folded" property and thus does not read on the limitations as recited in claims 51, 52, 54 and 58 (please see pages 4-5 of the arguments filed on 05/10/2006).

The applicant is pointed to the teachings of Fiedler et al wherein Fiedler et al teach the properties of antibody such as stability and antigen-binding activity. Even though Fiedler et al do not teach "correctly-folded polypeptide" per say, since Fiedler et al teach the stability and the functional properties of the antibody (abstract and results in particular), it is obvious that the antibodies produced by Fiedler et al are correctly-folded.

Further, the applicant argues, "the linker approaches used by each of the reference either do not work or are not designed to produce the claimed polypeptide". The applicant argues that "Hakim et al prepared the scFv with the (GGGGS)3 and... it did not work", and that the claimed polypeptide, which resembles a scFv (with a different linker) does work and has the claimed properties of a correctly folded protein.

Such arguments are found irrelevant to the current invention, because the claims are drawn to any linker that has between one and about 50 residues (but not a particular linker) which is clearly taught by the references cited. (Further, please see the response below).

Even though the claims recite any polypeptide, an appropriate argument cannot be presented by picking one linker that does not work in the art. The art clearly teaches the incorporation of any linker, for example Tang et al teach a method of selecting active scFvs synthesized from libraries of scFv genes with randomized linker DNA sequences (see abstract and pages 15682-15684, in particular) and that a linker suitable for one scFv will not be optimal for other scFvs and that the length of the linker and sequence affect the expression level, solubility, stability and binding affinity of the scFvs (see page 15682 column 2, in particular). Hence, one of ordinary skill in the art would have a reasonable expectation of success in using different linkers for different antibody molecules produced, because as taught by Tang et al, the linker sequence does affect the structural and functional properties of the antibody.

The applicant also states that it is clear that the binding ability alone is not sufficient and that the polypeptide needs an adjuvant to elicit an immune response.

In response to the above argument, the examiner agrees that Hakim et al teach that an adjuvant is important for a peptide to elicit an immune response, however is not required. As shown in figure 3 of Hakim et al show an increase the anti-Id titers by the scFv-IL-1β peptide alone; and thus it would have been obvious to one of ordinary skill in the art to would have known that such proteins can elicit an immune response.

3. The applicants argue that "the linkers in the library have certain limitations ..... even if a particular member of the two libraries may be the same the use of the respective linker libraries in different methods is different".

In response to such arguments, the applicant is reminded that the teaching of various of linkers to produce an scFv by Tang et al is sufficient to form a prima facie obvious rejection of the claims in view of Tang et al. The applicant is reminded that all that is required is that the prior art set forth the substance of the invention that tang et al teaches the method of selecting active scFvs synthesized from libraries of scFv genes with randomized linker DNA sequences. Thus, one of ordinary skill in the art would have been motivated and would and would have reasonable expectation of success to have used the linkers as taught by Tang et al and produce the polypeptide of the claimed invention.

4. The applicants argue that "claim 59 recites that the vector is transiently expressed in the cytoplasm ..... thus, the vector is permanently in the cell's nucleus of any regenerated plant selected to produce the polypeptide...".

In response to the above argument, the applicant is again reminded of the teachings of Fiedler et al teach two different scFv antibodies which were expressed in plants in different plant organs and plant cell compartments have been used for the study and further the expression of scFvs over a short period of time, Fiedler et al would still read on the claimed invention; please see the arguments as presented in paragraph 1 above.

5. The applicant argues that "claim 60 recites allowing the vector to spread throughout the plant and that the vectors used by Fiedler et al do not spread throughout the plant...".

In response to the above argument, the applicant is again directed to Fiedler et al wherein the Fiedler et al teach "that two different scFv antibodies which were expressed in plants in different plant organs and plant cell compartments", and thus would be read on the claim. In addition, the applicant is reminded of the teachings of Fiedler et al wherein Fiedler et al teach that scFv, which consists of variable light chain and variable heavy chain domain of an antibody molecule fused with a linker (see page 206 column 1, in particular), can be made in high quantities in transgenic plant cells, wherein 4-6% to 3-4% of the total protein found in soluble forms in leaves and seed, respectively, can be recombinantly expressed scFv.

In conclusion, based on the teachings on the prior art it would have been prima facie obvious to one of ordinary skill in the at the time the invention was made to have produced the polypeptide of the claimed invention because Hawkins et al teach the production of scFv molecules with a VH and VL joined by a linker, Caspar et al teach an scFv obtained from a B-cell lymphoma Ig surface antigen, which can induce an immune response (see page 3702 column 2, in particular), Tang et al teach scFvs comprising VH and VL domains linked by a randomized linker, Hakim et al teach immunotherapeutic compositions comprising a scFv constructed from the Ig variable

regions from B cell lymphomas (i.e., idiotype) for inducing a polyclonal anti-idiotype response that was protective against tumor challenge (see page 5503 column 2, in particular) and further because Fiedler et al teach the production of scFv in a plant.

It is noted that in the arguments presented on 08/10/2006 (page 7), the applicant states that the claims have been amended to encompass the concept of using many different linkers simultaneously in plants followed by screening for polypeptides with the specific abilities.

In response to above arguments, the claims do not specifically recite using many different linkers simultaneously and hence such argument is not found pertinent to the instant claims. Further, amending the claims to "a plurality of different linkers" does not change the scope of the invention as stated by the applicant. The art previously cited clearly teaches the method of producing polypeptides wherein the linker can be selected and optimized based on the polypeptide being produced. (for example, see Tang et al).

Further, the applicant is reminded that the amendment to the claim to include the screening of any polypeptide that induces an idiotype-specific immune response directed against the said polypeptide does not render the claims allowable, because the method as recited in claim 51 was never contemplated in the instant specification at the time of filing (please see the NEW MATTER rejection above).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 51-60 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4 and 10-13 of U.S. Patent No. 7084256 in view of Fiedler et al (Immunotechnology, 3(3):205-216, October 1997; IDS: March 08, 2004)

Claims 51-60 of instant application have been described supra.

Claims 1, 2 and 10-13 of U.S. Patent No. 7084256 (US 256) are drawn to a method of producing a polypeptide self-antigen useful as a tumor-specific vaccine in a subject with a B-cell lymphoma or at risk of developing a B-cell lymphoma, wherein a first domain and a second domain of the polypeptide self-antigen are encoded by at

least in part by a nucleic acid in the cells of said B-cell lymphoma, which polypeptide comprises two peptide domains connected to each other by a peptide linker, and said polypeptide includes an epitope or epitopes unique to, or overexpressed by, cells of said B-cell lymphoma, thereby distinguishing said B-cell lymphoma from normal cells and/or all other tumors (i) of the same or different histological type, (ii) in said subject or in another member of said subject's species, comprising the steps of: (a) joining a nucleic acid encoding the first domain of the polypeptide to a nucleic acid encoding a first part of a linker to produce a first nucleic acid construct; (b) joining the first nucleic acid construct encoding a second part of the linker to a nucleic acid encoding the second domain of the polypeptide to produce a second nucleic acid construct; (c) incorporating said second nucleic acid construct into a plant expression vector in frame so that, when expressed, the polypeptide bears the first and second domain separated by the linker; (d) transfecting a plant with the vector so that the plant is capable of producing the polypeptide; (e) producing the polypeptide; and (f) recovering the polypeptide as a soluble, correctly-folded protein, wherein the polypeptide recovered from said plant or plant cell is in correctly folded form, without a need for denaturation and renaturation and mimics said epitope or epitopes in their native form and is capable of inducing an immune response in a mammal, including said subject, without a need for adjuvant or other immunostimulatory materials, so that administration of said polypeptide results in an antibody or cell-mediated immune response to said epitope or epitopes, and wherein the polypetide is a single chain the first domain is the Ig V.sub.H domain and the second domain is Ig V.sub.L domain, both of which domains create an

idiotype of a surface Ig of said B cell lymphoma, and wherein said polypeptide induces an idiotype-specific response directed to said B-cell lymphoma upon administration to a subject, wherein the plant is a plant cell, wherein the plant expression vector is a transient plant expression vector that transiently produces the polypeptide. Further, claims 10-13 are drawn to the above- recited method, wherein said domains are linked by an amino acid linker that (a) has between one and about 50 residues; (b) consists of between one and 12 different amino acids, and (c) facilitates secretion and correct folding of said polypeptide to mimic the B-cell lymphoma epitope in its native form in or on said B-cell lymphoma cell, wherein the linker is a member of a randomized library of linkers that vary in size and sequence, and said library is encoded by nucleic acid sequences consisting of a repeated pattern of degenerate repeated triplet nucleotides having the following requirements; (i) position 1 of each repeated triplet cannot be the same nucleotide as position 2 of the repeated triplet; (ii) position 2 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet; or (iii) position 1 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet, wherein the nucleotide in the first and second positions of each repeated triplet is selected from any two of deoxyadenosine, deoxyguanosine, deoxycytidine or deoxythymidine,wherein (i) position 1 of each repeated triplet is deoxyadenosine or deoxyguanosine; (ii) position 2 of each repeated triplet is deoxycytidine or deoxyguanosine; and (iii) position 3 of each repeated triplet is deoxythymidine.

Claims 1, 2 and 10-13 of U.S. Patent No. 7084256 do not teach above method wherein the vector is transiently expressed in the cytoplasm further comprising after

transfecting the plant, allowing the vector to spread throughout the plant before recovering the polypeptide.

These deficiencies are made up for by Fiedler et al.

Fiedler et al teach two different scFv antibodies which were expressed in plants in different plant organs and plant cell compartments have been used for the study, in addition to investigating the levels and antibody properties such as stability and antigen-binding activity (abstract, in particular). Fiedler et al teach that scFv, which consists of variable light chain and variable heavy chain domain of an antibody molecule fused with a linker (see page 206 column 1, in particular), can be made in high quantities in transgenic plant cells, wherein 4-6% to 3-4% of the total protein found in soluble forms in leaves and seed, respectively, can be recombinantly expressed scFv. Furthermore, Fiedler et al teach that such recombinant scFv is functionally active (see page 214 column 1, in particular).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced the method as claimed, please see below.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have produced the method as claimed in claims 51-53 and 58, because claims 1 and 2 of US 256 are drawn to method of producing a polypeptide self-antigen useful as a tumor-specific vaccine in a subject with a B-cell

lymphoma or at risk of developing a B-cell lymphoma, wherein a first domain and a second domain of the polypeptide self-antigen are encoded by at least in part by a nucleic acid in the cells of said B-cell lymphoma, which polypeptide comprises two peptide domains connected to each other by a peptide linker, and said polypeptide includes an epitope or epitopes unique to, or overexpressed by, cells of said B-cell lymphoma, thereby distinguishing said B-cell lymphoma from normal cells and/or all other tumors (i) of the same or different histological type, (ii) in said subject or in another member of said subject's species, comprising the steps of: (a) joining a nucleic acid encoding the first domain of the polypeptide to a nucleic acid encoding a first part of a linker to produce a first nucleic acid construct; (b) joining the first nucleic acid construct encoding a second part of the linker to a nucleic acid encoding the second domain of the polypeptide to produce a second nucleic acid construct; (c) incorporating said second nucleic acid construct into a plant expression vector in frame so that, when expressed, the polypeptide bears the first and second domain separated by the linker; (d) transfecting a plant with the vector so that the plant is capable of producing the polypeptide; (e) producing the polypeptide; and (f) recovering the polypeptide as a soluble, correctly-folded protein, wherein the polypeptide recovered from said plant or plant cell is in correctly folded form, without a need for denaturation and renaturation and mimics said epitope or epitopes in their native form and is capable of inducing an immune response in a mammal, including said subject, without a need for adjuvant or other immunostimulatory materials, so that administration of said polypeptide results in an antibody or cell-mediated immune response to said epitope or epitopes, and wherein

the polypetide is a single chain the first domain is the Ig V.sub.H domain and the second domain is Ig V.sub.L domain, both of which domains create an idiotype of a surface Ig of said B cell lymphoma, and wherein said polypeptide induces an idiotype-specific response directed to said B-cell lymphoma upon administration to a subject, wherein the plant is a plant cell.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced the method as claimed in claims 54-57, because claims 10-13 of US 256 are drawn to the method of producing a polypeptide as in claim 1 of the patent, wherein said domains are linked by an amino acid linker that (a) has between one and about 50 residues; (b) consists of between one and 12 different amino acids, and (c) facilitates secretion and correct folding of said polypeptide to mimic the B-cell lymphoma epitope in its native form in or on said B-cell lymphoma cell, wherein the linker is a member of a randomized library of linkers that vary in size and sequence, and said library is encoded by nucleic acid sequences consisting of a repeated pattern of degenerate repeated triplet nucleotides having the following requirements; (i) position 1 of each repeated triplet cannot be the same nucleotide as position 2 of the repeated triplet; (ii) position 2 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet; or (iii) position 1 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet, wherein the nucleotide in the first and second positions of each repeated triplet is selected from any two of deoxyadenosine, deoxyguanosine, deoxycytidine or deoxythymidine,wherein (i) position 1 of each repeated triplet is deoxyadenosine or

deoxyguanosine; (ii) position 2 of each repeated triplet is deoxycytidine or deoxyguanosine; and (iii) position 3 of each repeated triplet is deoxythymidine.

Moreover, one of ordinary skill in the art would have known to produce a method of producing a polypeptide as recited in claims 59 and 60 by combining the above teachings with Fiedler et al, because Fiedler et al teach two different scFv antibodies which were expressed in plants in different plant organs and plant cell compartments have been used for the study, in addition to investigating the levels and antibody properties such as stability and antigen-binding activity (abstract, in particular); and further that the plant expression system as discussed in their studies, provides not only the highest level of active single chain Fv antibodies ever reported but also a short-term storage of the foreign protein in the harvested plant material, which suggests that the plant expression system as taught by Fiedler et al still reads on the transient plant expression vector, in addition to that antibody molecule can be made in high quantities in transgenic plant cells, wherein 4-6% to 3-4% of the total protein found in soluble forms in leaves and seed, respectively, can be recombinantly expressed scFv (see page 206 column 1, in particular). Thus, since the expression vector as taught by Fiedler et al provides for a short-term storage of the foreign protein in the harvested plant material, it reads on the limitation as recited in claim 59 and 60.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

13. No claims are allowed

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi, Ph.D.
Ph: (571) 272-8789

SHEELA HUFF
PRIMARY EXAMINER